Thyroid Crisis:

Diagnosis and Treatment

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THYROID crisis is an uncommon complication of thyrotoxicosis, but is of particular interest to surgeons because it may either complicate operative management of hyperthyroidism or may co-exist in patients with other surgical problems. Current treatment for thyroid storm, although more effective than in the past, is controversial and there is disagreement over criteria for diagnosis. These considerations prompted the present study. A review and analysis of 21 instances of thyroid crisis seen during the past 19 years at the Charity Hospital of Louisiana at New Orleans served as a basis for this report.

Material

Two thousand, three hundred and twenty-nine patients were admitted to Charity Hospital with the diagnosis of hyperthyroidism between January 1, 1949 and January 1, 1968. Twenty-one had thyrotoxicosis classified as thyroid storm.

Although there were 625 operations for thyrotoxicosis during this period, only one of the 21 patients developed storm postoperatively. This patient survived a crisis which followed bilateral subtotal thyroidectomy for Graves' disease. The only other patient with postoperative crisis died after total gastrectomy performed for Zollinger-Ellison syndrome. Table 1 shows the yearly admissions and number of operations for hyperthyroidism and the associated occurrence of thyroid crisis over the period of study.

No increased seasonal incidence of thyroid crisis was seen (Fig. 1). There was a preponderance of women and Negroes as might be expected from the increased incidence of hyperthyroidism in women, and the predominance of Negroes in the hospital population (Table 2). The youngest patient was 20 years old and the oldest 73. Most patients were between 30 and 71 years of age (Fig. 2).

Clinical data are shown in Table 3. All patients were severely ill with extreme toxicity and only five of 21 survived. No patient had the clinical picture of apathetic storm.

There was some apparent factor which precipitated thyroid crisis in 13 patients. This was most often infectious disease, and in two was related to surgical operation (Table 4).

Thirteen patients who died underwent autopsy. Hyperplasia of the thyroid was present in all, and thyromegaly was found in all but one. Cardiomegaly, pulmonary edema and bronchopneumonia were common. Hepatic changes were not consistent, but congestion of the liver was frequent. Autopsy findings are summarized in Table 5.

Objective documentation of thyrotoxicosis was requisite for inclusion in this series. Characteristic changes in thyroid function tests, autopsy confirmation of thyroid hyperplasia and physical findings such as en-

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TABLE 1. *Admissions and Number of Operations for Hyperthyroidism and Occurrence of Thyroid Crisis, 1949–1967*

Year	No. of Admissions	Operations	Cases of Thyroid Crisis
1949	100	44	1
1950	129	61	
1951	86	51	1
1952	100	51	1
1953	99	37	
1954	65	22	2
1955	67	49	
1956	110	25	1
1957	93	28	
1958	108	22	2
1959	112	27	2
1960	99	31	1
1961	141	23	2
1962	156	41	2
1963	154	25	
1964	210	28	1
1965	218	12	2
1966	156	18	2
1967	126	30	1
Total	2329	625	21

docrine exophthalmos or goiter with bruit, were accepted in this regard (Table 6).

Discussion

What constitutes thyroid crisis and what criteria should be applied to make this diagnosis, has always been of concern. McArthur *et al.*[9] said that thyroid storm represents a state in which the patient can no longer tolerate the strain imposed by thyrotoxicosis, and reaches the point where hyperthyroidism is "life-endangering." This concept points up the lack of a unique factor which identifies thyroid storm other than accentuation of the thyrotoxic state.

TABLE 2. *Sex and Race Distribution of Cases of Thyroid Crisis, 1949–1967*

	Male	Female	Totals
Negro	4	14	18
White	1	2	3
Totals	5	16	21

This strain characteristically leads to decompensation of thermoregulatory mechanisms, cardiopulmonary dynamics, or possibly the liver.

In many patients associated illnesses or stresses provide the stimulus to precipitate runaway hyperthyroidism. In most instances these factors have some continuing effect beyond the point where storm begins, and it is often difficult to separate the specific effect of concomitant disease from the effect of thyrotoxicosis. This has led [10] to questions of whether or not severe hyperthyroidism with associated complicating disease should be considered thyroid storm. Careful evaluation of most thyroid crises will reveal some associated disorder. Whether this disorder caused, complicated, or came about because of thyroid storm is often not apparent. There are thus few "pure" thyroid crises, and within the scope of the definition of thyroid crisis as a life-endangering exacerbation of hyperthyroidism, it seems that cases with non-thyroidal associated illnesses may properly be called storms.

In this review a patient was considered to be in thyroid crisis only if the clinical course was accompanied by abnormal thyroid function tests, characteristic physical findings such as goiter with bruit or exophthalmos, or autopsy evidence of thyroid hyperplasia. Our concept of the clinical picture of thyroid storm is that described by Lahey,[5] and consists of severe anxiety and agitation, progressing in many cases to extreme weakness, disorientation, delirium, coma and death. Although Lahey states that pyrexia is not an invariable accompaniment of storm,[5] it is generally regarded as characteristic,[4] and extreme degrees are recorded. Nine of the 21 patients in this series had temperatures of 40.6° C. or higher, and one patient had a temperature of 42.4° C. Fever is not a normal finding in uncomplicated thyrotoxicosis, and its presence is indicative of either an associ-

TABLE 3. *Clinical Data on Patients at Time of Thyroid Crisis*

Patient	Age	Sex	Survival	Temp. (°C)	Pulse Rate	Goiter	Sensorium	Vomiting	Diarrhea	Jaundice	Congestive Heart Failure
D. A.	27	F	Died	40.6	124	+	Agitation, delirium, coma	+	0	0	+
L. S.	39	F	Died	42.2	160	+	Agitation	+	+	0	+
N. L.	53	F	Survived	39.9	110	+	Agitation, disorientation	0	0	0	0
D. H.	45	F	Died	40.6	164	+	Agitation	+	0	+	+
L. O.	48	F	Died	40.8	186	+	Agitation, delirium, coma	0	0	0	+
G. N.	50	F	Died	Not Recorded	160	+	Agitation, delirium, coma	0	+	0	0
C. R.	64	F	Died	38.9	160	+	Agitation	0	0	0	+
N. W.	37	F	Died	40.6	200	+	Not Recorded	+	0	0	0
E. C.	64	F	Died	38.6	190	+	Agitation	0	0	0	0
J. S.	65	M	Died	40.6	200	+	Agitation, disorientation	0	+	0	+
A. M.	64	F	Died	39.4	204	+	Agitation, disorientation	+	0	0	0
D. D.	30	F	Survived	40.0	128	+	Delirium	+	+	0	0
A. W.	50	M	Died	40.2	196	+	Agitation, delirium, coma	+	+	+	+
M. Sa.	33	F	Died	40.0	156	+	Agitation, delirium, coma	+	+	0	0
M. W.	42	F	Died	40.6	120	+	Agitation, delirium, coma	0	0	+	0
E. D.	73	M	Died	41.1	160	0	Agitation, disorientation	+	+	0	0
J. B.	32	M	Died	39.4	280	0	Agitation, delirium, coma	0	0	0	+
J. M.	20	M	Survived	39.4	184	+	Agitation	0	0	0	0
R. W.	51	F	Survived	40.2	130	0	Agitation, delirium	0	0	0	+
M. McG.	49	F	Died	41.7	184	+	Agitation, delirium, coma	0	0	0	+
M. So.	43	F	Survived	38.7	138	+	Agitation, delirium	+	0	0	+

ated illness or of an abnormality of thermal regulation.

Other findings associated with thyroid storm such as vomiting, diarrhea or congestive heart failure were not present in all of the patients. The presence or absence of these symptoms or signs or of azotemia, hypoglycemia, jaundice or dehydration were not regarded as essential to the diagnosis of thyroid storm.

Clinical evidence of hepatic decompensation, occurred in only three patients although several autopsies showed some liver abnormalities. Passive congestion was common, and central lobular necrosis was seen in only 2 instances. This observation is simi-

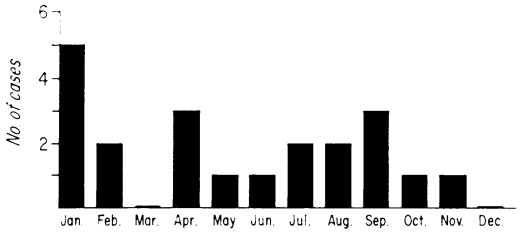

FIG. 1. Distribution by month of cases of thyroid crisis from January 1, 1949, through 1967.

lar to that of others,[6, 17] and does not support a specific role of the liver in thyroid crisis.[2]

Five patients had thyroid function tests during crisis. Radioactive iodine uptake (RAIU) was measured in three and all were abnormally high. In two of these three patients, antithyroid drug treatment was given after the tracer dose of ^{131}I, and it is difficult to interpret results. One patient had a 6 hour RAIU determined before treatment and a strikingly high 63% uptake was found. Two of the three patients who had ^{131}I uptake tests also had triiodothyronine (T_3) resin uptake measurements performed. Both were abnormally high at 48% and 54%, respectively.

Three patients had protein bound iodine (PBI) determinations during crisis and all were elevated. The values were 8.9, 13.9, and 19.0 $\mu g\%$. This wide variation has been noted by others, and is not completely understood.[6, 16] The lowest value of 8.9 $\mu g\%$ was measured in a patient whose crisis occurred after total gastrectomy for the Zollinger-Ellison syndrome. The rapid onset of crisis in that instance suggests that T_3 may have been the principal thyroid hormone responsible for the hypermetabolic state. Triiodothyronine is much more physiologically active than thyroxine on a weight basis, and is also less tenaciously bound to carrier proteins in the plasma. For these reasons, if T_3 were the principal hormone causing a thyrotoxic state, PBI values would be lower than might be expected with severe thyrotoxicosis. This may explain findings in one patient, and those of others who reported relatively low PBI values during thyroid crisis.

The problem of differential diagnosis was well illustrated by this study. Eight patients thought to have had thyroid storms were found at autopsy to have normal thyroid glands. In each of these there were significant pathologic changes in other organ systems responsible for the clinical features mistaken for thyroid crises. Severe bronchopneumonia was most often incorrectly diagnosed as storm, and one patient had overwhelming sepsis from a primary infection at an amputation site. The following case is illustrative.

Case Reports

Case 1. A 67-year-old woman with a past history of toxic nodular goiter was admitted severely ill and in semicoma. Relatives stated that she had been ill for many months with nervousness, depression and weight loss. Her husband died suddenly 5 days before and she then developed agitated depression, dyspnea, and diarrhea. Fever and prostration followed and she rapidly worsened to a state of semicoma, severe dyspnea, and high fever.

She was cachetic and extremely toxic with an obtunded sensorium. Vital signs were as follows: temperature 39.1° C., pulse 204/min., respiration

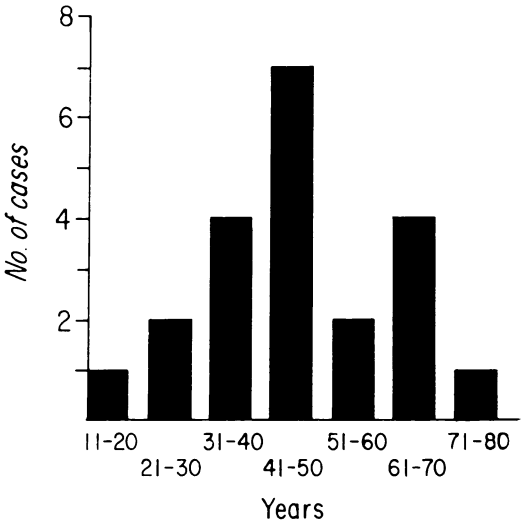

FIG. 2. Age distribution of patients with thyroid crisis from January 1, 1949, through 1967.

50/min. and blood pressure 110/70. The left lobe of the thyroid was enlarged and there was marked jugular vein distention despite dehydration. The heart was normal except for marked tachycardia. There were bilateral crepitant rales at the lung bases posteriorly, and sibilant rales at the right apex.

Chest x-ray showed an infiltrate in the right upper lung field thought to be active tuberculosis, and an EKG showed auricular flutter. The hemogram was normal and there was a 1+ albuminuria. The sputum contained only occasional gram positive diplococci and no acid fast organisms.

The presumptive diagnosis was thyroid crisis with congestive heart failure. Treatment included intravenous fluids, nasal oxygen, digoxin, a mercurial diuretic, antibiotics, and measures to lower temperature. Methimazole, sodium iodide, hydrocortisone sodium succinate and reserpine were also given. Shortly after admission, temperature rose to 41.2° C. She rapidly deteriorated and died 23 hours after admission.

Autopsy showed acute necrotizing hemorrhagic bronchopneumonia with microabscess formation. There was generalized fibrosis of the thyroid with the few remaining acini showing no evidence of hyperplasia.

Because of such occurrences objective substantiation of hyperthyroidism was required before a patient was classified as having thyroid storm. The past history of thyrotoxicosis and the clinical picture, however, indicated that thyroid storm was probably the major problem, and treatment was directed at thyroid crisis.

Postoperative Thyroid Crisis

The use of antithyroid drugs to establish a euthyroid state before operation has virtually eliminated thyroid crisis following thyroidectomy for hyperthyroidism. Only one instance of post thyroidectomy storm occurred over the last 19 years although 625 operations for thyrotoxicosis were performed. Several operations, however, were followed by minor febrile reactions which were not life endangering. Whether these might be classified as "storms in miniature," [9] or were due to other causes of postoperative fever, such as atelectasis or pneumonitis, cannot be determined. Many cases could be disregarded, however, since postoperative thyroid crisis almost always occurs shortly after operation, and fever 16 hours after operation is almost invariably due to other causes.[9]

TABLE 4. *Apparent Precipitating Factors in Patients with Thyroid Crisis*

Patient	Apparent Precipitating Factor
L. S.	Gastroenteritis
N. L.	Pharyngitis
C. R.	Bronchopneumonia
N. W.	Upper respiratory tract infection
E. C.	Bronchopneumonia
J. S.	Bronchopneumonia
A. M.	Acute pyelonephritis-bronchopneumonia
M. Sa.	Bronchopneumonia
M. W.	Pneumonia
E. D.	Gastroenteritis
J. M.	Thyroidectomy for Graves' disease
R. W.	Acute myocardial insufficiency
M. M.	Total gastrectomy for Z-E syndrome

Case 2. A 20-year-old man was seen in February, 1965, after two months of increasing nervousness, hyperhidrosis, exophthalmos and a 15-pound weight loss in spite of a good appetite. He weighed 108 pounds and had signs of hyperthyroidism with an elevated ^{131}I uptake (44%). He was given methimazole 40 mg. daily. In March, he seemed better although his weight was still 108 pounds. Methimazole dosage was increased to 80 mg. daily and he was given Lugol's solution, three drops three times a day. One month later, his weight was 110 pounds and his pulse rate was 72/min.

He was admitted for thyroidectomy in June. The dose of Lugol's solution was changed to 10 drops three times a day, and methimazole to 40 mg. daily. He weighed 104 pounds and his sleeping pulse rate was 80/min. He was also given chlordiazepoxide because of increasing apprehension about his operation. At 8:00 a.m. on June 21, bilateral subtotal thyroidectomy was done without incident. The operation was completed at 10:00 a.m. with the patient in good general condition. At 2:00 p.m. he became extremely restless and his pulse rate rose to 184/min., respiratory rate to 38/min., and blood pressure to 150/50. Temperature was 39.4° C. Because of extreme agitation, abrupt temperature increase, tachycardia and tachypnea, he was thought to be in thyroid crisis. Treatment with nasal oxygen, intravenous sodium iodide and hydrocortisone sodium succinate; intramuscular reserpine, digoxin and morphine was

TABLE 5. *Autopsy Findings in Patients Dying of Thyroid Crisis*

Patient	Thyroid	Heart	Lungs	Liver	Other
L. S.	75 Gm., nodular microscopic hyperplasia	420 Gm. Hypertrophy	1,400 Gm. Pulmonary edema	1,825 Gm. Fatty degeneration Congestion of sinusoids Portal cirrhosis	Acute splenic hyperplasia and congestion
D. H.	75 Gm., diffuse microscopic hyperplasia	400 Gm. Hypertrophy	1,275 Gm. Pulmonary edema	1,185 Gm. Passive congestion	
L. O.	200 Gm., diffuse microscopic hyperplasia	275 Gm. Dilated rt. ventricle	1,180 Gm. Pulmonary edema Bronchopneumonia	1,160 Gm. Passive congestion Central lobular necrosis	Generalized lymphoid hyperplasia
G. N.	129 Gm., diffuse microscopic hyperplasia	300 Gm. "Normal"	475 Gm. Diffuse atalectasis	950 Gm. Periportal cirrhosis	Squamous cell carcinoma of cervix (not spread)
C. R.	70 Gm. diffuse microscopic hyperplasia	240 Gm. Minimal interstitial myocarditis	820 Gm. Pulmonary edema Bronchopneumonia	990 Gm. Cirrhosis	Severe exophthalmous with corneal ulceration
N. W.	60 Gm. diffuse microscopic hyperplasia	250 Gm. Hypertrophy Myocardial fibrosis	650 Gm. Bronchopneumonia	1,625 Gm. Early fatty changes	Minimal cerebral edema
E. C.	55 Gm. diffuse microscopic hyperplasia	250 Gm. Hypertrophy	520 Gm. Pulmonary edema Bronchopneumonia	1,100 Gm. "Normal"	
J. S.	"Enlarged," nodular microscopic hyperplasia	250 Gm. Myocardial fibrosis	1,500 Gm. Pulmonary edema (marked) Bronchopneumonia	1,300 Gm. Passive congestion	
A. M.	99 Gm., nodular microscopic hyperplasia	400 Gm. Left ventricular hypertrophy	1,800 Gm. Pulmonary edema Bronchopneumonia	1,850 Gm. Passive congestion Severe central lobular congestion	Acute pyelonephritis
A. W.	50 Gm., diffuse microscopic hyperplasia	470 Gm. Dilation and hypertrophy	1,300 Gm. Pulmonary edema	1,320 Gm. Severe central lobular congestion; hepatocellular necrosis in half of central zones	
M. Sa.	76 Gm., diffuse microscopic hyperplasia	400 Gm. Left-ventricular hypertrophy	1,520 Gm. Pulmonary edema Bronchopneumonia	1,700 Gm. Passive congestion	Cerebral edema
E. D.	20 Gm., microscopic hyperplasia	300 Gm. Myocardial fibrosis	825 Gm. Bronchopneumonia	1,100 Gm. Minimal fatty change	
M. McG.	210 Gm., diffuse microscopic hyperplasia	500 Gm. Left-ventricular hypertrophy	1,230 Gm. Pulmonary edema	2,300 Gm. Passive congestion	Residual islet cell tumor in wall of duodenum. Cerebral edema

instituted. Aspirin was given by rectum and alcohol sponging and ice bags were applied to control pyrexia. By 11:30 p.m. he was less restless, temperature was 38.1° C. and pulse rate was 118/min. He steadily improved and both reserpine and morphine were discontinued the next afternoon. Cortisone dosage was rapidly decreased and he was discharged from the hospital on June 29.

Preoperative failure to gain weight and considerable apprehension about operation indicated potential problems with this patient and should have led to a more careful assessment of his metabolic state. Treatment in thyroid crisis was well directed. Since there was no perpetuating associated

illness, and since thyroidectomy effectively removed a continuing source of thyroid hormone, recovery was rapid and complete.

The other instance of postoperative thyroid crisis followed gastrectomy.

Case 3. A 49-year-old woman with a history of duodenal ulcer was admitted May 3, 1966 with upper gastrointestinal bleeding. She was given 1,500 ml. of blood and bleeding ceased. X-rays showed a duodenal ulcer. Bleeding recurred on May 11, but stopped after 1,000 ml. of blood was given. Two successive 12-hour overnight gastric analyses yielded acid outputs of 110 and 215 mEq. The diagnosis of Zollinger-Ellison syndrome was made.

Thyroid enlargement, which had been present on a previous admission was again noted. A PBI determination in December, 1965, was reported as 6 μg./100 ml. One observer believed that she was "borderline hyperthyroid," but recurrent bleeding with anemia made this clinical diagnosis equivocal.

A large duodenal ulcer was found at laparotomy on May 26. A polypoid duodenal tumor was also found and adjacent lymph nodes contained tumor cells of metastatic islet cell carcinoma. A total gastrectomy was done. She did well immediately postoperatively, but the next morning, was febrile (38.9° C.) and dyspneic. Atelectasis was suspected, and intermittent positive pressure breathing was started. Respiratory distress became progressively worse and pulmonary edema developed. Morphine, aminophylline and digoxin were given but she did not improve. A tracheostomy was necessary by midafternoon on May 28. That evening she had an attack of acute anxiety. Her pulse rate was 150/min. and she was thrashing about wildly in bed. Morphine and hydroxyzine were given intravenously. Two hours later temperature had risen to 41.7° C. and there was marked tachypnea and tachycardia. The possibility of thyroid crisis was considered, and intravenous hydrocortisone sodium succinate and sodium iodide were given. Alcohol sponging and dipyrone did not affect the temperature, and the patient became unresponsive and hypotensive. She died at 1:25 a.m. on May 29.

At autopsy there was marked pulmonary edema and the liver was congested and friable. The thyroid was diffusely enlarged and weighed 210 grams. Microscopic examination showed hyperplasia. A PBI determination on blood drawn just prior to iodide administration was reported after death at 8.9 μg./100 ml.

The diagnosis of hyperthyroidism was considered before gastrectomy because of thyroid enlargement and persistent tachycardia. Laboratory confirmation was not sought and this possibility was dismissed. Late in the course severe thyrotoxicosis was thought to be present but the patient died before an effect of therapy could be detected. Irrespective of mild hyperthyroidism before operation, this case demonstrates how stress of a major surgical procedure can precipitate thyroid crisis, and the disastrous results of severe uncontrolled postoperative thyrotoxicosis.

Treatment

In thyroid crises it is possible to discern different aspects of the disorder which need specific treatment. The thyroid gland itself is one of these in overproduction of thyroid hormones and the effects of those hormones on the body. Decompensated organ systems, such as the heart and lungs, is another aspect of the syndrome, and the third is precipitating or perpetuating illnesses.

The thyroid gland can be dealt with both by interfering with the formation of thyroid hormone, and by blocking hormone release. Drugs such as methimazole or propylthiouracil (PTU) block the intrathyroidal organification of iodide and thus interfere with the production of thyroid hormone. One of these drugs should be given in large doses as soon as the clinical diagnosis of thyroid storm is made. Methimazole 20 to 30 mg. every 6 hours, or PTU 300 mg. every 6 hours may be used. Both drugs must be given by mouth since there are no parenteral preparations. A stomach tube may be necessary in an uncooperative or unconscious patient.

Iodides should then be used to block release of preformed thyroid hormone, and to a lesser degree, interfere with hormone synthesis. Sodium iodide may be given intravenously by infusion using as much as two or three grams in 24 hours.

TABLE 6. *Documentation of Hyperthyroidism in Patients with Thyroid Crisis*

Patient	Documenting Criteria
D. A.	Goiter with bruit; BMR's +82 and +69 two months prior to admission
L. S.	Goiter with hyperplasia (Autopsy)
N. L.	Goiter with bruit; BMR's +62 and +63 two months prior to admission
D. H.	Goiter with hyperplasia (Autopsy); BMR +60 six months prior to admission
L. O.	Goiter with hyperplasia (Autopsy); BMR +62 two months prior to admission
G. N.	Goiter with hyperplasia (Autopsy)
C. R.	Goiter with hyperplasia (Autopsy); 24 hr. RAIU 61% two days prior to crisis
N. W.	Goiter with hyperplasia (Autopsy); 24 hr. RAIU 96% four months prior to crisis
E. C.	Goiter with hyperplasia (Autopsy); BMR over +100 two weeks prior to crisis
J. A.	Goiter with hyperplasia (Autopsy); 24 hr. RAIU 69% during crisis
A. M.	Goiter with hyperplasia (Autopsy); 24 hr. RAIU 57% one day prior to crisis
D. D.	Goiter with bruit; BMR +75 three months prior to admission
A. W.	Goiter with hyperplasia (Autopsy); PBI 13.9 μg% during crisis
M. Sa.	Goiter with hyperplasia (Autopsy)
M. W.	Goiter (no bruit) 24 hr. RAIU 76% four days prior to crisis
E. D.	Normal size thyroid with hyperplasia (Autopsy); 24 hr. RAIU 48% and T_3 resin uptake 68% one week prior to crisis
J. B.	Exophthalmos; 24 hr. RAIU 75% four months prior to crisis
J. M.	Goiter with bruit; Thyroid hyperplasia (surgical specimen); 24 hr. RAIU 44% four months prior to crisis
R. W.	24 hr. RAIU 45%, T_3 resin uptake, 54%, PBI 19 μg% at onset of crisis
M. M.	Goiter with hyperplasia (Autopsy); PBI 8.9 μg% at onset of crisis
M. So.	Goiter (no bruit); six hr. RAIU 63% and T_3 resin uptake 48% during crisis

There is a possible advantage in delaying the use of iodides until about an hour after either methimazole or PTU has been given. Theoretically without the ongoing effect of the antithyroid drugs to stop hormone synthesis iodide might serve as additional substrate material for thyroid hormone. The rapid involutional effects of iodides are, however, far more important to the immediate crisis state than the more delayed effects of antithyroid drugs. Iodides should not be withheld if for some reason it is impossible to use either methimazole or PTU.

In association with the direct suppression of thyroid activity, simultaneous efforts should be made to alter the effects of thyroid hormone on the body. Excessive thyroid hormone increases peripheral sensitivity to circulating catecholamines. This sensitivity to adrenergic stimuli is responsible for many of the symptoms and signs of thyrotoxicosis, and crisis has been characterized as the result of an acute adrenergic outburst.[3] An effort to suppress these effects is important.

Reserpine or guanethidine are most effective in this regard. Reserpine causes release of tissue stored catecholamines, but blocks their effects. This drug should be given in large amounts by intramuscular injection, and 2.5 mg. may be used as often as every 4 to 6 hours. At this dose level there is also a significant sedating effect, which is desirable in an agitated patient.

Guanethidine blocks release of catecholamines from post-ganglionic adrenergic nerves, and thus diminishes circulating levels of epinephrine and norepinephrine. It should also be used in large doses and up to 100 or 200 mg. may be given each day. This drug must be given by mouth, and although onset of action is prompt, its effectiveness may be impaired by vomiting or diarrhea. Guanethidine does not have the sedative effect of reserpine, and other drugs should be added if this is desired.

Sympathetic blockade can also be achieved by spinal anesthesia. This technic has been used in the treatment of thyroid crisis,[12] but it is doubtful that it offers material advantages over reserpine or guanethidine.

The need to support failing organ systems is often apparent in thyroid crisis. Fever, which has been termed the sine qua non of thyroid storm,[4] is evidence of decompensation of heat regulatory mechanisms. Cardiac failure is frequent, and hepatic involvement with jaundice often occurs during crisis.[1, 2, 6, 7, 17] Central nervous system decompensation is also common and most patients show extreme agitation, progressing in some to delirium and coma.

Fever control measures are important and include alcohol sponging, application of ice bags, or use of an ice mattress. The cool environment of an oxygen tent has been recommended[13] but it is difficult to keep a hyperactive patient in one of these devices. Specific antipyretic drugs like aspirin, sodium salicylate or dipyrone are also useful.

Digitalis, bronchodilators, sedation and even phlebotomy may be necessary when heart failure occurs. Drugs such as atropine should not be used to control secretions, however, since they also release the vagal brake on the heart rate. Oxygen therapy is helpful, and although it has been recommended in thyroid crisis to compensate for increased metabolic demands, it is probably most helpful for related heart failure.

Diminished glycogen reserves have been detected in patients with thyroid storm,[1, 2] and biochemical evidence of hepatic derangement is common. Glucose should be provided for protective effect on the liver, and to supply calories. Water soluble vitamins should be used liberally.

Whatever sedation is necessary is often supplied by reserpine. Morphine and barbiturates can also be used, but it is probably best to use an agent which can be readily counteracted. It may be difficult to distinguish the effects of sedation from progression of the disease to coma, and sedative induced respiratory depression should be avoided. Small parenteral doses of morphine titrated to need, are preferable.

Most authors[4, 8, 10, 14, 17, 18] believe the use of cortisone or similar drugs is important in the treatment of thyroid storm. Routine use has however, been characterized as therapeutic abuse.[3] Undoubtedly the use of steroids is abused in many illnesses and possibly in thyroid crisis. It is doubtful that most illnesses, no matter how severe, overtax the ability of normal adrenal glands to meet the body needs for glucocorticoids. There is however, objective evidence that thyrotoxicosis increases the reduction and conjugation rate of adrenal steroids,[15] and that secretion rates are increased.[11] For these reasons, and since the short-term use of large doses of cortisone seldom leads to harm, it seems best not to withhold steroids in the face of thyroid crisis.

When glucocorticoids are used, the dose should be the amount which the adrenal glands would be expected to secrete under maximal stress. For hydrocortisone this is approximately 300 mg. in 24 hours, and if one of its analogues is used, the dose should be comparable.

The significance of associated disease, and the difficulties with both diagnosis and treatment, was apparent in the patients reviewed in this series. In eight of 13 autopsies there was an associated infectious process. All these patients had bronchopneumonia, and one also had acute pyelonephritis. Pulmonary infections were suspected in only two.

In two of the remaining five patients autopsied, it was thought prior to death that acute infections were present. One patient was suspected of having acute bacterial endocarditis, and the other acute pelvic inflammatory disease. Neither autopsy confirmed these diagnoses.

The review of this autopsy material, together with the clinical case histories, leads to the inescapable conclusion that it is difficult to diagnose accurately the presence or absence of infections during thyroid crisis. It is recommended that patients suspected

of thyroid storm be given large doses of broad spectrum antibiotics. It is important to obtain appropriate cultures before antibiotic treatment so that if pathogens are recovered, antibacterial therapy can be changed depending on sensitivity studies. The view that antimicrobial treatment should be withheld in thyroid storm pending identification of a septic process,[4] seems restrictive in view of the findings in this series.

The clinical course of one patient illustrates the application of treatment principles discussed.

Case 4. A 51-year-old woman was admitted in September, 1966, because of intractable angina pectoris and congestive heart failure. Symptoms of nervousness, fatigue and palpitations, had been present for two months, and she lost 15 pounds over this period. She was restless and perspired excessively. Her blood pressure was 170/90, pulse rate 110/min., respiration 22/min., and temperature 37.3° C. The thyroid was not enlarged.

Despite treatment with digitalis, diuretics, bed rest and analgesics, chest pain and low grade fever continued, and although myocardial infarction was suspected, there were no diagnostic EKG changes.

Twelve days after admission temperature rose to 39.4° C. and she developed supraventricular tachycardia resistant to diphenylhydantoin, hydroxyzine and lanatoside C. Fever and tachycardia persisted and she became extremely agitated and disoriented and lapsed into coma. Thyroid crisis was suspected and blood for a PBI and T_3 resin uptake was drawn. A tracer dose of ^{131}I was given, and treatment was begun. Oxygen was administered by nasal catheter and she was given 50 mg. of methimazole followed in 2 hours by ten drops of Lugol's solution. Methimazole was continued at 50 mg. every 12 hours and one gram of sodium iodide was give by infusion every 12 hours. Reserpine 0.5 mg. intramuscularly and guanethidine 50 mg. by mouth were given every 12 hours. Methyl prednisolone sodium succinate was given by infusion to a dose of 125 mg. every 24 hours, and three Gm. of ampicillin daily were given by the same route. Parenteral digoxin was substituted for digitalis. All oral medication had to be given by nasogastric tube.

Temperature control measures included aspirin suppositories, alcohol sponging, intramuscular dipyrone and the use of an ice mattress. Shortly after treatment was begun her temperature rose further to 40.4° C. and in spite of therapy, remained above 38.9° C. for the next 48 hours.

She remained comatose for approximately 72 hours, but then began to regain consciousness. Temperature came down to 37.8° C. at this time and became normal the next day. She improved considerably over the next 24 hours and it was possible to remove the nasogastric tube and begin oral feedings. Steroid dosage was rapidly decreased and antibiotics were stopped 8 days after storm began. She was continued on methimazole and remained in the hospital an additional two weeks. Angina did not recur after the crisis.

Thyroid function studies done at the onset of storm were as follows: PBI 19 μg./100 ml., T_3 resin uptake 54%, and 24 hour RAIU 45%.

Systematic well directed treatment resulted in survival of this severely ill patient. The different aspects of the clinical syndrome were each given special attention based on an understanding of the pathophysiology. In retrospect, this patient's intractable angina was probably caused by unrecognized thyrotoxicosis.

The survival of only five of 21 patients (24%) is probably due to different factors. Perhaps the most significant is that all but two can be classified as "medical" thyroid storms, since there was no associated operative procedure. Patients with "medical" thyroid crisis are usually older than those with "surgical" storm and most often have associated diseases which are more severe than the operative trauma associated with thyroidectomy. In addition, thyroidectomy is a self-limiting aspect since most of the thyroid is removed.

The patients of Charity Hospital often tend to seek medical attention at an advanced stage of illness, and long neglected medical problems are commonplace. This also may have played a role in the low survival rate.

Another factor in the low survival rate involves the rigid criteria which had to be met before a patient was classified as having storm. Several patients with thyrotoxicosis and febrile illnesses were not included because retrospective analyses did

not indicate that there was a life-endangering situation. Other surviving patients were not included because there was no objective documentation of hyperthyroidism.

The net result of only 24% survival shows no improvement when compared to the series of McArthur *et al.*,[9] and is far from the 70% reported by Waldstein *et al.*[17] Three of the last four patients survived, however, and such seriously ill patients as patient 4 reported above can withstand thyroid crisis if systematically and vigorously treated.

Summary and Conclusions

Twenty one instances of thyroid crisis during the last 19 years at Charity Hospital of Louisiana at New Orleans are reported. Only two followed operations. Rigid objective criteria for the diagnosis of thyroid crisis were used. Sixteen patients died and 13 were autopsied. The incidence, precipitating factors, clinical course, treatment and clinicopathologic correlations were assessed. The differential diagnosis of thyroid crisis was examined and highlighted by other cases which mimicked thyroid storm.

Although uncommon, thyroid storm is still a serious problem in clinical medicine. Differential diagnosis from other illnesses can be difficult, and since delay in beginning therapy can be harmful, patients suspected of having thyroid storm should be so treated without awaiting objective confirmation of crisis. Adrenocortical steroids, antithyroid drugs, reserpine or guanethidine, sedation, antibiotics, and temperature control measures are all efficacious. Decompensation during crisis of overstressed organ systems, commonly the cardiorespiratory complex, is to be anticipated and vigorous specific treatment should be initiated at the first sign that this has occurred. Uncontrolled associated illness, most often respiratory, is important in precipitating thyroid storm, and is a major cause for treatment failure.

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